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N.E.
39. (Amended) A process for making a vaccine composition for the use in the method of Claim 1, comprising admixing (a) an adjuvant composition comprising a surfactant of formula (I), (b) a pharmaceutically acceptable excipient, and (c) an antigen or antigenic composition.

REMARKS

Claims 1-24, 30, 32-35 and 37 are pending in the instant application. Claims 1-24, 30, 32-35 and 37 stand rejected. The specification, Claims 19-20, 20(a) and 21 are objected to. The Applicants herein cancel Claims 2-3, 18-24, 29-33, 35-37 and 40-41 without prejudice and amend Claims 1, 4-17, 25-28, 34 and 38-39. Claims 1, 4-17, 25-28, 34 and 38-39, as amended, find support in the specification at page 2, lines 11-16; page 3, line 19 to page 6, line 19; page 7, line 26 to page 8, line 15, and elsewhere. Accordingly, no new matter is raised by this amendment. The Applicants also amend the specification to include a section entitled "Brief Description of the Drawings" in accordance with the Examiner's instructions. In view of the following amendment and response, the Applicants believe the claims presented herein are allowable. Reconsideration is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

OBJECTIONS

In the Office Action, the Examiner notes the lack of a brief description of the drawings. In response to the Examiner's note, the Applicants have inserted a separate section titled "Brief Description of the Drawings" after the "details of the invention" and before the "Examples." This amendment renders this objection to the specification moot and the Applicants respectfully request its withdrawal.

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The Examiner also alleges that there are two claims numbered "Claim 20". The Applicants apologize to the Examiner for their oversight when they made the Preliminary Amendment on September 29, 2000. But because the Applicants have since canceled Claims 18-24, this objection is now moot. The Applicants again respectfully request its withdrawal.

The Examiner further notes spelling errors in Claims 21 and 35. As these claims are now canceled, these objections are likewise moot.

The Examiner finally alleges that Claims 19, 20 and 20(a) are improper multiple dependent from other multiple dependent claims. Because these claims are canceled in the instant response, this objection is moot and its withdrawal is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-3, 7, 8, 10,13-20, 20(a), 21, and 32-35 are rejected under 35 U.S.C. §112, first paragraph, as allegedly being based on a specification which does not contain an adequate enabling written description of the invention. Claims 2-3, 18-21, 32-33 and 35 are canceled, therefore rendering the rejection moot for these claims.

At page 3, line 1, the Examiner rejects Claim 1 for allegedly failing to describe in the specification a composition wherein the surfactant is in the form of a "micelle." The Applicants respectfully traverse. It is well known in the art of surface chemistry that a micelle is a colloidal aggregate of amphipathic (surfactant) molecules, which occurs at a well-defined concentration known as the critical micelle concentration. It is also well known that the typical number of aggregated molecules in a micelle (aggregation number) is 50 to 100. *See, for example, <http://surfactants.net/micelle.htm>*, a copy of which is provided herewith. Therefore, a person of ordinary skills in the art reading the teachings of the instant specification will understand the meaning of "micelles" and the method of making and using them. Nevertheless, the Applicants have amended Claim 1 to no longer recite "micelle",

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therefore rendering this rejection under 35 U.S.C. §112, first paragraph moot, and they respectfully request its withdrawal.

At page 3, line 12 of the Office Action, the Examiner further alleges that the term "pathogenic infections" and "cancer" are inclusive of a wide variety of diseases of different etiologies and the prior art does not establish that all of the encompassed diseases are effectively treated/prevented with the instantly claimed vaccine. The Applicants respectfully traverse this allegation and assert that it is well known in the art that all cancers and opportunistic infections are caused by compromises of one's immune system. Normal immune system equips one with natural killer cells that are capable of recognizing malignant cell masses and invading pathogens and clearing these matters. *See, for example, Lodish, et al., Molecular Cell Biology*, third edition, Scientific American Books, Inc., page 1296 at lines 9-12 and column 2; and page 1309, column 2 (1995), a copy of which is provided herewith. The instantly claimed method increases immune response and hence the body's ability to recognize and clear infectious pathogens and cancer cells, alleviating or preventing illnesses. Therefore, a person of ordinary skills in the art would grasp through the teachings of the instant application that the claimed method can be used to treat or prevent cancers as well as pathogenic infections.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejects claims 15 and 30 as allegedly being indefinite. At page 3, line 20, the Examiner alleges that in Claim 15, the term "selected from the group comprising" is inconsistent with the accepted Markush group terminology. The Applicants have since amended Claim 15 to recite the Markush language suggested by the Examiner and thus respectfully request the withdrawal of this rejection.

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Claim 30 is canceled, thus rendering the rejection moot. The Applicants likewise request the withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

REJECTIONS UNDER 35 U.S.C. § 102(b) AND ALTERNATIVELY § 103(a)

Claims 1-24, 30, 32-35 and 37 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by or in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over each of 1) Brown; 2) Ullman, *et al.*; 3) Teerlink, *et al.*; 4) Berezin, *et al.*; 5) Longenecker, *et al.*; 6) Fontan, *et al.* (chemical abstract); 7) Rinella, *et al.*; 8) Morein, *et al.*; 9) Modi; 10) Moste-Deshairs, *et al.*; 11) De Vries, *et al.*; 12) Modi-2, *et al.*; 13) Glass, *et al.*; 14) Proteus; 15) Micro Vesicular; 16) Frontan-2, *et al.*; 17) Singh, *et al.*. Claims 2-3, 18-24, 30, 32-33, 35 and 37 are canceled. Claims 1, 4-17 and 34 stand rejected. The Applicants respectfully traverse.

Each of these references is addressed below:

1) **Brown.** The Applicants respectfully assert that Brown neither anticipates nor makes obvious the instant claims. A single prior art reference anticipates a claimed invention only if it identically shows every element of the claimed invention. *In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Brown teaches the creation of a respirable aerosol spray of bovine gammaglobulin, rather than a vaccine composition, as instantly claimed. Therefore, Brown does not anticipate the current claims under 35 U.S.C. § 102(b).

For a proper obviousness rejection under 35 U.S.C. § 103(a), the Examiner has the burden of establishing *prima facie* with evidence or reason that, *inter alia*, at the time of the invention, (1) the prior art of record would have suggested or motivated one of ordinary skill in the art to carry out the combination and modification of the prior art as suggested by the Examiner to arrive at the claimed invention, and (2) "the prior art would also have revealed that in so making or carrying out, those of ordinary skill in the art would have a reasonable expectation of success. The suggestion or motivation and the reasonable expectation of

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success must be found in the prior art, not in the appellant's disclosure. *In re Vaek*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Brown teaches the making of an aerosol spray that is suitable to deliver bovine gammaglobulin in particle sizes that are sufficiently small to be respirable. It teaches the use of non-ionic surfactants to produce propellant-driven aerosols, but does not teach the delivery of vaccines, let alone using these surfactants as adjuvant to enhance the immune response in humans. Seeking to induce human immunity intranasally, a person skilled in the art would only be motivated to look for a potential adjuvant, but not an apparatus or agent that would deliver a bovine protein. Therefore, the instant claims are not obvious over Brown.

2) Ullmann, et al. Ullmann, *et al.* describe the interaction between surface active polyoxyethylene ethers and nicotinic acid esters, but not the use of these ethers or esters in delivering vaccine intranasally in order to increase immune responses. It therefore does not anticipate the instant claims under 35 U.S.C. § 102(b).

Further, the knowledge of how the ethers and esters interact, where the interaction takes place is far removed from the use of polyoxyethylene ethers as an adjuvant that increases the immune response. Delivery of vaccine intranasally and effectively involves an entirely different set of issues as merely studying how ester droplets are formed. Therefore, no person skilled in the art learning that the interaction occurs outside the micelle could logically predict that a vaccine composition would be effective if these esters or ethers were incorporated. Therefore, the instant claims are not obvious over Ullmann, *et al.*

3) Teerlink, et al. Teerlink *et al.* find that detergents enhance the immune response synergistically with the adjuvant activity of aluminum phosphate (AlPO₄). They did not disclose the increased immune response induced by the detergents themselves, as instantly claimed. Thus, Teerlink, *et al.* do not anticipate the instant claims.

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Further, mice were injected with the vaccine-AlPO₄-detergent complex intraperitoneally, whereas the antigen was either adsorbed to AlPO₄ or not adsorbed. The authors find that the many-fold increase in immune responses is caused by the adsorption of the vaccine to AlPO₄, rather than the use of surfactants. As adsorption of the vaccine to AlPO₄ would dictate that the vaccine cannot be made into a spray or an aerosol and is thus unfavorable to be administered intranasally, a person skilled in the art would not be motivated by Teerlink, *et al.* to test the detergent-AlPO₄ combination when he seeks to improve immunogenicity of a vaccine that is intended to be administered intranasally.

Therefore, Teerlink, *et al.* do not render the instant claims obvious.

✓ 4) Berezin, et al. Berezin, *et al.* use detergents to solubilize viral glycoproteins that are necessary in the production of a vaccine. At page 450, column 2, sections titled "Purification of glycoproteins"; "Preparation of liposomes"; and at page 451, "Formation of glycoprotein complexes with the glycoside Quil A", Berezin, *et al.* describe a vaccine preparation procedure that eventually removes the detergent by centrifugation and dialysis into PBS. Therefore, no detergent was administered to the subject animals at all. Therefore, Berezin, *et al.* fail to anticipate the instant claims, which clearly administer the detergent to the subject as an adjuvant.

In fact, Freund's complete adjuvant (Difco) was used as an adjuvant as described at page 451, in the section entitled "Immunization of animals." Therefore, the success in inducing immune response by Berezin, *et al.* can be attributed to the solubilized liposomes and the Freund's adjuvant, but not any surfactants listed in Table 1. A person skilled in the art following the teachings of Berezin, *et al.* would have carefully centrifuged and dialyzed out the surfactants so that they would not harm the subjects during immunization. Moreover, the subject animals were immunized subcutaneously with the vaccine, rather than intranasally, rendering it unobvious to one skilled in the art, who seeks to increase the immune response of an intranasally administered vaccine, to consult Berenzin, *et al.* as a reference. Thus, Berezin, *et al.* do not render the instant claims obvious.

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5) Longenecker, et al. Longenecker, *et al.* teach the use of surfactants in intranasal delivery of insulin, but not a vaccine. Because insulin is a self-antigen, its administration to a subject is not intended or expected to induce auto-immunity in the subject. In contrast, one intends and expects to induce or enhance immunity in the subject when he administers a vaccine. The delivery of insulin and the delivery of a vaccine composition are thus very different, albeit both intranasally delivered. As a result, Longenecker, *et al* do not anticipate the instant invention.

Neither do Longenecker, *et al.* render the instant invention obvious under 35 U.S.C. § 103(a). One skilled in the art reading the teachings of Longenecker, *et al.* would understand that the reagents used by Longenecker, *et al.* would not act as an adjuvant to induce or enhance an immune response as it is clearly undesirable to induce the subject's auto-immunity during an insulin injection. Therefore, Longenecker, *et al.* teach away from using surfactants such as Laureth-9 in inducing an immune response in the subject, as it is instantly claimed. A person skilled in the art reading the teachings of Longenecker, *et al.* will likely steer clear of the described surfactants because he is seeking to enhance the subject's immune response with the vaccine. Hence, the instant claims are not obvious over Longenecker, *et al.* under 35 U.S.C. § 103(a).

6) Fontan, et al. (chemical abstract) Fontan, *et al.* describe the use of polyethylene ethers and polysorbates as adjuvants in suppositories, rather than intranasal vaccines, as claimed in the instant application. It therefore does not anticipate the instant claims.

It is also well known in the art that suppositories differ from intranasal pharmaceutical applications in the method of administration, likelihood of complications and mechanism of adsorption. The most apparent difference is in the application of these drugs, intranasally administered drugs are sprayed or applied to the nostrils, while suppositories are administered through the rectum, vagina, and urethra. The rectum, for example, is an unusual area for drug absorption because it is not buffered and has a neutral pH. There is also very little enzymatic activity, thus no enzymatic degradation. The rectal mucosa is also more capable than mucosa in other parts of the body of tolerating various drug-related irritations. The anorectal

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physiology provides a large surface area for drug absorption. The surface area is also permeable to non-ionized drugs. Suppositories can be used with a variety of different bases to increase absorption and reduce complications, partly because the chemicals taken up by the veins in the rectal areas bypass the liver and do not undergo first-pass metabolism. *See, for example, <http://www.gw labs.com/round.jsp>*, a copy of which is provided herewith.

Administration of medicine through the nostril cavities is much more technically demanding because of the small area of adsorption, liver toxicity concerns and the presence of multiple proteolytic enzymes. Therefore, Fontan, *et al.* would not have motivated a person ordinarily skilled in the art seeking to administer a vaccine intranasally and induce immunogenicity to use the same adjuvant as what is in a suppository, especially where the components of the suppository have only been tested *in vitro*. That skilled person would have found no reasonable expectation of success in this reference, and therefore Fontan, *et al.* do not render the instant claims obvious.

✓ 7) Rinella, et al. Rinella, *et al.* teach the use of surfactants in eluting antigens that are absorbed to aluminum-containing adjuvants and are otherwise irreversibly bound. At page 48, column 1, in the paragraph entitled "Introduction", Rinella, *et al.* point out that their paper addresses the need to elute the antigens for *in vitro* testing of vaccines. The criteria used to select surfactants are therefore the effectiveness of these surfactants in removing preadsorbed proteins and their abilities to cause protein denaturation. Therefore, Rinella, *et al.* fail to disclose **any** element of the current invention, which is directed to a vaccine composition that is to be administered to a person, let alone every element as it is required for anticipation under 35 U.S.C. §102(b).

Further, Rinella, *et al.* do not render the instant claims obvious because a person skilled in the art searching for an effective intranasally deliverable vaccine formula would not be motivated to use a method that merely washes off the antigen from the adjuvant, but does nothing to enhance immune responses. The Applicants hereby respectfully request that the Examiner withdraw his rejection under 35 U.S.C. § 103(a) based on Rinella, *et al.*.

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✓ 8) Morein. Morein discloses a process of preparing an immunogenic complex called iscom. *See, for example*, column 1, lines 5-6. It is known in the art that iscoms are vaccine formulations that combine a multimeric presentation of antigen with a built-in adjuvant. It has a cage-like structure composed of *Quillaja* saponins, cholesterol, phospholipids, and protein. Typically, iscoms have icosahedral symmetry, are 30-40 nm in diameter, and are composed of 12-nm ring-like subunits. *See, for example*, <http://www.bmc.uu.se/virology/iscoms.html>, a copy of which is provided herewith ; *see also* Höglund, *et al.*, *Iscoms and immunostimulation with viral antigens*. In: *Subcellular Biochemistry* (Ed. Harris, J. R.) Plenum, New York, pp. 39-68 (1989). Thus, the *Quillaja* is the adjuvant, not surfactants, as they are in the instantly claimed invention. Morein therefore does not anticipate the instant claims under 35 U.S.C. § 102(b).

Neither does Morein render the instant claims obvious. The procedure of making iscoms comprises solubilization of amphipathic proteins in preferably nonionic detergents, addition of *Quillaja* saponins, cholesterol, and phosphatidylcholine. In the presence of amphipathic proteins, iscom particles are formed on removal of the detergent. But if no protein (antigen) is present in the mixture, then iscom matrix is formed. *Id.* A person skilled in the art reading Morein would actively remove the surfactant to ensure formation of the iscom particles because these particles form the adjuvant. The instant claims, however, are directed to a vaccine composition comprising a detergent, whereas the detergent is administered to the subject and actually improves the intranasal delivery of the vaccine and enhances the immunogenicity. A person skilled in the art seeking to improve intranasal delivery and immunity therefore would not be motivated to use the reagents for the iscoms and would not reasonably expect success if he follows the teachings of Morein. Therefore, Morein does not render the instant claims obvious under 35 U.S.C. § 103(a).

✓ 9) Modi, et al. (US6,221,378) Modi, *et al.* teach the use of absorption enhancing compounds including lecithin, hyaluronic acid, octylphenoxy polyethoxyethanol, etc., which, in combination with a conventional micellar composition, form mixed micelle liposomal solutions. *See, for example*, column 10, lines 3-5, 20-24. These liposomes are vesicles, thus

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are different from the solution or non-vesicular solution or suspension claimed by the instant claims. Modi, *et al.* do not therefore identically disclose every element of the Applicants' invention and do not anticipate the instant claims under 35 U.S.C. § 102(b).

Further, Modi, *et al.* do not render the instant invention obvious because they do not motivate or encourage a person skilled in the art to use the disclosed method in the development of an aqueous solution vaccine. As disclosed in the instant specification at page 5, lines 20-26, having a vaccine composition in a solution form would eliminate the usual problems associated with manufacturing a capsulated or vesicular formula, namely the lack of stability, uniformity and quality control. Therefore, the instant claims are not obvious over Modi, *et al.* under 35 U.S.C. § 103(a).

✓ 10) Moste-Deshairs, et al. Moste-Deshairs, *et al.* do not anticipate the instant claims as they do not identically disclose every element of these claims. Moste-Deshairs, *et al.* teach the making of a vaccine composition against influenza and the viral core using a surfactant at column 3, line 65 to column 4, line 48; as well as in Example 4, particularly at column 4, lines 25-26 and column 10, lines 26-27. Accordingly, surfactants such as Triton X-100 or Brij 36T were removed by centrifugation and resuspension of pellets in PBS. In contrast, the instant application claims an intranasal vaccine formulation comprising the polyoxyethylene ether or ester surfactant. The surfactant must be present for the instantly claimed method to yield and enhanced immune response. Therefore, Moste-Deshairs, *et al.* do not anticipate the instant claims under 35 U.S.C. § 102(b).

Moste-Deshairs, *et al.* also do not render the instant claims obvious because a skilled artisan reading the teachings of Moste-Deshairs, *et al.* would have removed the surfactants by centrifugation or dialysis as disclosed and his resulting vaccine composition would not include a surfactant. No motivation and expectation of success would be engendered by Moste-Deshairs, *et al.*. Therefore, the instant claims are not obvious under 35 U.S.C. § 103(a) over Moste-Deshairs, *et al.*

✓ 11) De Vries, et al. Like Morein in 8) above, De Vries, *et al.* teach the making of an iscom vaccine. The vesicular form of the iscom particles are clearly shown in Figure 1 and 2. As

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the instant claims are directed to a non-vesicular vaccine composition, and for the same reasons illustrated in 8), the Applicants respectfully assert that De Vries, *et al* neither anticipate the instant claims under 35 U.S.C. § 102(b) nor render the instant claims obvious under 35 U.S.C. § 103(a).

12) Modi, et al. (US 5,653,987) Modi, *et al.* disclose a liquid pharmaceutical agent formulation suitable for nasal delivery of drugs with **at least two** absorption enhancing compounds that include EDTA, oleic acid, linoleic acid, polyoxyethylene X-lauryl ether, etc. At column 6, particularly lines 51-54 and Table III, Modi *et al.* show that the orally administered insulin formulation that only contains one absorption enhancer has little metabolic effect on the blood glucose level. Therefore, Modi, *et al.* do not teach the use of a single surfactant polyoxyethylene X-lauryl ether in a vaccine composition as instantly claimed, and as a result do not anticipate the instant claims under 35 U.S.C. § 102(b).

In fact, Modi, *et al.* teach away from using a single surfactant in making a vaccine that is intranasally deliverable because they found that at least two surfactants must be present before the vaccination becomes effective. As the instant claims are directed to the method of enhancing immune response using a single surfactant, directly against the teachings of Modi, *et al.*, the instant claims are not obvious under 35 U.S.C. § 103(a) over Modi, *et al.*.

✓ 13) Glass, et al. The instant claims are not anticipated by Glass, *et al.* because Glass, *et al.* do not identically disclose every element. Glass, *et al.* teach an adjuvant comprising non-ionic surfactants in a water-in-oil or oil-in-water emulsion form. In contrast, the instant claims are directed to an adjuvant that is an aqueous solution (*see, for example*, page 6, lines 24-27 of the instant specification). Therefore, Glass, *et al.* do not anticipate the instant claims under 35 U.S.C. § 102(b) as its claimed surfactants must be enclosed in the oil phase of the adjuvant.

Neither do Glass, *et al.* render the claimed invention obvious because person skilled in the art seeking to make a soluble, easily filter-sterilizable and easily manufactured vaccine would not be motivated to use the same reagents that makes a water-in-oil or an oil-in-water

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emulsion. Indeed, Glass, *et al.* teach away because their results engender an expectation in the person skilled in the art that using the disclosed reagents would yield a vaccine in a water-in-oil or an oil-in-water emulsion, rather than an aqueous solution. Thus, the instant claims are not obvious over Glass, *et al.* under 35 U.S.C. § 103(a).

14) Proteus. Proteus teaches the use of non-ionic surfactant in making a vaccine in a vesicle form. The instant claims, on the other hand, are directed to a vaccine composition that is a non-vesicle solution. Thus, Proteus does not anticipate the instant claims under 35 U.S.C. § 102(b).

Further, Proteus does not render the instant claims obvious because person skilled in the art would not expect success in using the reagents disclosed in Proteus to make a vaccine composition that is in solution, easily purified and have none of the usual problems associated with manufacturing vaccines comprising particulate or vesicular adjuvant systems. Thus, the instant claims are not obvious over Proteus.

15) Micro Vesicular. Like Proteus, Micro Vesicular teaches a vaccine that is a vesicle, rather than a non-vesicle solution, as it is instantly claimed. Therefore, Micro Vesicular neither anticipates the instant claims under 35 U.S.C. § 102(b) nor render the instant claims obvious under 35 U.S.C. § 103(a).

16) Fontan, et al. Similar to Fontan, *et al* (chemical abstract) addressed in 5) above, Fortain, *et al.* here teach the making of a vaccine suitable for use as suppositories. Because of the vast differences in the mechanism of adsorption between nasal mucosa and the rectal, vaginal or urethra mucosal linings, Fontan, *et al.* do not anticipate the instant claims under 35 U.S.C. § 102(b) or render the claims obvious under 35 U.S.C. § 103(a).

17) Singh, et al. Claims 1-13 and 15-17 are rejected under 35 U.S.C. § 102(b), or alternatively, under 35 U.S.C. § 103(a) as obvious over Singh, *et al.* Claims 2-3 are canceled, thus Claims 1, 4-13 and 15-17 stand rejected. The Applicants respectfully traverse this rejection. Singh, *et al.* teach the use of various surfactants in herbicides, rather than intranasally administering a vaccine to a human subject. There is no reason to expect a person of ordinary skill in the art of vaccine development to look to the art of herbicide for

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guidance on vaccine toxicity and physiological effects. The Applicants respectfully assert that administering chemicals to plant leaves and roots with the intention to kill the plant is surely and vastly distinct from administering chemicals to a person with the intention to cure his diseases or keep him alive. Therefore, Singh, *et al.* do not anticipate the instantly claimed invention under 35 U.S.C. § 102(b).

Further, Singh, *et al.* do not render the instant claims obvious for two reasons: 1) a person skilled in the art would not look to Singh, *et al.* as a reference when he seeks to make a vaccine because the making of herbicide is not from the same field of endeavor; and 2) the disclosed technology is not reasonably related to the particular problem with which the inventor is involved. "References that are too remote to be treated as prior art" should not be used to render an invention obvious. *In re Clay*, 966 F.2d 656, 658 (Fed. Cir. 1992) (quoting *Panduit Corp. v. Dennison Mfg.*, 810 F.2d 1561, 1568 n. 9 (Fed. Cir. 1987), *cert. denied*, 481 U.S. 1052, 107 S.Ct. 2187, 95 L.Ed.2d 843 (1987)).

A maker of herbicides does not seek to enhance the immunity of weeds, but seeks to kill them, while the maker of a vaccine seeks to enhance the survival of a vaccinated subject by inducing the person's immunity to pathogens or diseases. Further, plant metabolism and mechanism of growth are different from that of the mammals. Therefore, vaccine making falls within the art of pharmaceutical development whereas herbicide making falls within plant sciences and agriculture engineering. A person skilled in the art of designing a vaccine will not look for suitable agents from the art of plant science, especially not an agent that is used in killing plants. The technology described by Singh, *et al.* is also not reasonably related to the particular problem the Applicants here were seeking to address, namely the induction of enhanced immune response in a human subject. Therefore, the art of making a herbicide would not have logically commanded itself to the skilled person's attention in making a human vaccine and the skilled person surely would not have consulted the herbicide-making references and applied the teachings when he wants to induce immunity in humans. The instant claims are thus not obvious over Singh, *et al.* under 35 U.S.C. § 103(a).

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In view of the foregoing amendment and remarks, the Applicants respectfully assert that the prior art references cited by the Examiner do not anticipate or render the instant claims obvious, taken alone or in combination. The Applicants hereby respectfully request the withdrawal of these rejections under 35 U.S.C. § 102(b), and alternatively, 35 U.S.C. § 103(a).

The Applicants reserve the right to prosecute, in one or more patent applications, the claims as originally filed and any other claims supported by the specification. The Applicants thank the Examiner for the Office Action and consideration of this response. In view of the above amendment and remarks, which the Applicants believe are fully responsive to the outstanding Office Action, the Applicants respectfully request reconsideration of the rejected claims and allowance of all claims in the application. The Examiner is invited to contact the Applicants' undersigned attorney at the number provided below if this might facilitate prosecution of this case.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW WHERE CHANGES MADE

IN THE SPECIFICATION:

Insert a section entitled "Brief Description of the Drawings" at page 16 of the specification, before the paragraph "--The present invention is illustrated by, but not restricted to, the following examples.--" as follows:

Brief Description of the Drawings

Figure 1 shows the anti-OspA responses in mice of Example 2.

Figure 2 shows the LA2 titres in mice of Example 2.

Figure 3 shows anti-OspA responses in mice of Example 3.

Figure 4 shows LA2 titres in mice of Example 3.

Figure 5 shows Anti-OspA antibody titres in mice of Example 4.

Figure 6 shows LA2 titres in mice of Example 4.

Figure 7 shows anti-TT immunoglobulin responses as measured by ELISA of Example 5.

Figure 8 shows anti-FHA immunoglobulin responses as measured by ELISA of Example 5.

Figure 9 shows anti-OspA ELISA titres in AGM's of Example 6.

Figure 10 shows LA2 titres in AGM's of Example 6.

Figure 11 shows intranasal priming and boosting of AGM's, anti-OspA ELISA responses of Example 7.

Figure 12 shows intranasal priming and boosting of African Green Monkeys with POE and CpG vaccine formulations (of Example 8) and nasal induction of systemic Abs to lipo OspA in monkeys.

Figure 13 shows intranasal priming and boosting of African Green Monkeys with POE and CpG vaccine formulations (of Example 8) and induction of nasal IgA to lipo OspA in monkeys.

Figure 14 shows intranasal boosting of mice with POE-9LE and CpG vaccine formulations (of Example 9) and nasal boosting of serum IgG.

Figure 15 shows intranasal boosting of mice with POE-9LE and CpG vaccine formulations (of Example 9) and nasal boosting of serum LA2 Abs.

Figure 16 shows serum IgG responses to Lipo-OspA in mice of Example 10.

Figure 17 shows serum LA2 titres in mice of Example 10.

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Figure 18 shows serum IgG response to influenza virus A/Singapore/6/86 in mice of Example 11.

Figure 19 shows serum IgG Abs to influenza virus A/Beijing/262/95 in Africa Green monkeys of Example 12.

Figure 20 shows serum IgG response to PS14 in mice of Example 13.

Figure 21 shows serum IgG response to PS19 in mice of Example 13.

Figure 22 shows serum IgG responses to Lipo-OspA in mice of Example 14.

Figure 23 shows serum LA2 titers in mice of Example 14.

IN THE CLAIMS:

1. (Amended) A[n] method of raising an immune response in an individual against an antigen or antigenic composition, comprising administering intranasally to said individual a vaccine composition comprising an adjuvant composition and an antigen or antigenic composition; wherein the adjuvant composition is selected from the group consisting of: a non-vesicular aqueous solution and a suspension of [comprising] a surfactant of formula (I): $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{-A-R}$

wherein, n is 1-50, A is a bond or $-\text{C}(\text{O})-$, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl[; and a pharmaceutically acceptable excipient, characterized in that the surfactant of formula (I) is in the form of an aqueous solution or a micelle].

4. (Amended) A[n] adjuvant composition as claimed in any one of claims 1 to 3, characterised in that] method of raising an immune response as claimed in Claim 1, wherein the surfactant of formula (I) is haemolytic.

5. (Amended) A[n] adjuvant composition comprising] method of raising an immune response as claimed in Claim 1, wherein the adjuvant composition comprises a surfactant of formula (I): $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{-A-R}$, wherein[, n is 1-50, A is a bond or $-\text{C}(\text{O})-$, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl, and a pharmaceutically acceptable excipient, characterized in that the surfactant of formula (I) is not in the form of a vesicle and also in that the degree of haemolytic activity is in the range of 0.05-0.0001% as measured in the Guinea Pig blood haemolysis assay.

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6. (Amended) A[n adjuvant] method of raising an immune response as claimed in Claim 4 or Claim 5, wherein the surfactant of formula (I) has a haemolytic activity within a ten fold difference to that of polyoxyethylene-9 lauryl ether or polyoxyethylene-8 stearyl ether, as measured in the Guinea Pig blood haemolysis assay.

7. (Amended) A[n adjuvant composition] method of raising an immune response as claimed in any one of the Claims 1 [to] and 4-6, using an adjuvant that comprises [comprising] a surfactant of formula (I), wherein n is 4 to 24.

8. (Amended) A[n adjuvant composition] method of raising an immune response as claimed in any one of Claims 1 [to] and 4-7, wherein the adjuvant comprises [comprising] a surfactant of formula (I), wherein R is C₈₋₂₀ alkyl or Phenyl C₈₋₂₀ alkyl.

9. (Amended) A[n adjuvant composition comprising] method of raising an immune response as claimed in Claim 1, wherein the adjuvant comprises a surfactant of formula (I): HO(CH₂CH₂O)_n-A-R, wherein n is 9, A is a bond or -C(O)-, R is C₁₋₅₀ alkyl or Phenyl C₁₋₅₀ alkyl; and a pharmaceutically acceptable excipient, characterized in that the surfactant of formula (I) is not in the form of a vesicle.

10. (Amended) A[n adjuvant composition] method of raising an immune response as claimed in Claims 8 or 9, wherein R is C₁₂ alkyl.

11. (Amended) A[n adjuvant composition] method of raising an immune response as claimed in Claim 1 comprising a surfactant of formula (I): HO(CH₂CH₂O)_n-A-R, wherein n is 8, A is a bond or -C(O)-, R is C₁₋₅₀ alkyl or Phenyl C₁₋₅₀ alkyl; and a pharmaceutically acceptable excipient, characterized in that the surfactant of formula (I) is not in the form of a vesicle.

12. (Amended) A[n adjuvant composition] method of raising an immune response as claimed in Claim 11, wherein R is C₁₈ alkyl.

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13. (Amended) A[n adjuvant composition as claimed in any one of claims 1 to 12,] method of raising an immune response as claimed in Claim 1 comprising a surfactant of formula (I), wherein A is a bond, thereby forming an ether.

14. (Amended) A[n adjuvant composition as claimed in any one of claims 1 to 12,] method of raising an immune response as claimed in Claim 1 comprising a surfactant of formula (I), wherein A is -C(O)-, thereby forming an ester.

15. (Amended) A[n adjuvant composition] method of raising an immune response as claimed in Claim 1, wherein the polyoxyethylene ether or ester of formula (I) is selected from a group [comprising] consisting of: polyoxyethylene 9-lauryl ether, polyoxyethylene-9-lauryl ester, polyoxyethylene-9-stearyl ether, polyoxyethylene-8-stearyl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether and polyoxyethylene-23-lauryl ether.

16. (Amended) A[n adjuvant composition as claimed in any one of claims 1 to 15,] method of raising an immune response as claimed in Claim 1, wherein the concentration of the surfactant is in the range of 0.1-10%.

17. (Amended) A[n adjuvant composition as claimed in claim 16,] method of raising an immune response as claimed in Claim 1, wherein the concentration of the surfactant is in the range of 0.25-1%.

25. (Amended) A [vaccine composition comprising an adjuvant composition as claimed in any one of claims 1 to 24,] method of raising an immune response as claimed in Claim 1, further comprising an antigen or antigenic composition.

26. (Amended) A [vaccine as claimed in claim 25,] method of raising an immune response as claimed in Claim 1, wherein the antigen or antigen composition is derived from the group [comprising] consisting of: Human Immunodeficiency Virus, Varicella Zoster virus, Herpes Simplex Virus type 1, Herpes Simplex virus type 2, Human cytomegalovirus,

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Dengue virus, Hepatitis A, B, C or E, Respiratory syncytial virus, human paplloma virus, Influenza virus, Hib, Meningitis virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Streptococcus, Mycoplasma, Mycobacteria, Haemophilus, Plasmodium or Toxoplasma, IgE peptides such as the stanworth decapeptide[; or] and Tumor associated antigen (TMA) such as MAGE, BAGE, GAGE, MUC-1, Her-2 neu, LnRH, CEA, PSA, KSA, or PRAME.

27. (Amended) A [vaccine composition comprising] method of raising an immune response as claimed in Claim 1, wherein the vaccine comprises polyoxyethylene-9 lauryl ether and an influenza virus antigen.

28. (Amended) A [vaccine as claimed in any of claims 25 to 27] method of raising an immune response as claimed in Claim 1, wherein the vaccine is in the form of an aerosol or a spray.

34. (Amended) A spray device, more particularly a bi-dose spray device, filled with a vaccine [characterised in that the vaccine comprises: (a) a surfactant of general formula (I): $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{-A-R}$, wherein, n is 1-50, A is a bond or $-\text{C}(\text{O})-$, R is C₁₋₅₀ alkyl or Phenyl C₁₋₅₀ alkyl; (b) a pharmaceutically acceptable excipient; and (c) an antigen or antigenic composition.] suitable for use in the method of raising an immune response as claimed in Claim 1.

38. (Amended) A method of [treating] treatment, using the method of Claim 1, of a mammal suffering from or susceptible to a group of diseases consisting of: a pathogenic infection, cancer and allergy, comprising the intranasal administration of a safe and effective amount of a vaccine composition according to Claims 25-28.

39. (Amended) A process for making a vaccine composition [according to any one of claims 25 to 28,] for the use in the method of Claim 1, comprising admixing (a) an adjuvant composition [as claimed in any one of claims 1 to 24,] comprising a surfactant of formula (I), (b) a pharmaceutically acceptable excipient, and (c) an antigen or antigenic composition.